Efficacy and safety of omalizumab in patients with chronic urticaria who exhibit IgE against thyroperoxidase

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Background: A subgroup of patients with chronic spontaneous urticaria (CU) exhibits IgE antibodies directed against autoantigens, such as thyroperoxidase (TPO). We conducted this study to investigate whether such patients with CU with IgE against TPO benefit from treatment with omalizumab, a humanized anti-IgE mAb licensed for the treatment of severe persistent allergic (IgE-mediated) asthma.

Objectives: We sought to assess the efficacy of omalizumab treatment in patients with CU with IgE autoantibodies against TPO.

Methods: In this multicenter, randomized, double-blind, placebo-controlled study patients with CU (male/female, 18-70 years of age) with IgE autoantibodies against TPO who had persistent symptoms (wheals and pruritus) despite standard antihistamine therapy were randomized to receive either omalizumab (75-375 mg, dose determined by using the approved asthma dosing table) or placebo subcutaneously once every 2 or 4 weeks for 24 weeks. The primary end point was the change from baseline in mean weekly urticaria activity score after 24 weeks of treatment, as calculated from patients' diaries. The safety and tolerability of omalizumab were also assessed.

Results: Of the 49 randomized patients (omalizumab, n = 27; placebo, n = 22), 42 completed the study. At week 24, patients demonstrated a mean reduction in the weekly urticaria activity score from baseline of 17.8 with omalizumab and 7.9 with placebo ($P = .0089$). Complete protection from wheal development was observed in 19 (70.4%) patients in the omalizumab group compared with only 1 (4.5%) patient in the placebo group. The rate of adverse events was similar in both groups.

Conclusions: The results of this study indicate that omalizumab is an effective treatment option for patients with CU with IgE autoantibodies against TPO who are refractory to conventional treatment. (J Allergy Clin Immunol 2011;128:202-9.)

Key words: *Urticaria, wheals, pruritus, mast cells, anti-IgE, antihistamine, CU-Q2oL*

Chronic spontaneous urticaria (CU) is a common and disabling disease characterized by recurrent, itchy, wheal and flare–type skin reactions; angioedema; or both.[1] H_1-antihistamines are the mainstay of symptomatic therapy. However, less than half of patients with CU achieve sufficient symptom control with antihistamines at standard doses, the only licensed treatment for CU.[2,3]

CU symptoms are brought about by the degranulation of skin mast cells. During the past decade, several mechanisms of mast cell activation in CU have been identified. For example, IgG autoantibodies directed against IgE, which are detectable in a subset of patients with CU, can cause cross-linking of mast cell–bound IgE and subsequent mast cell degranulation.[4,5] Another subgroup of patients with CU exhibits IgG autoantibodies directed against the α-subunit of the high-affinity IgE receptor FcεRI on mast cells.[4,6,7] Very recently, we have identified a subgroup of patients with CU who exhibit IgE autoantibodies against thyroperoxidase (TPO), and IgE antibodies against TPO (IgE–anti-TPO)–positive patients with CU exhibit significantly higher

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Abbreviations used

AE: Adverse event
AUC: Area under the curve
CU: Chronic spontaneous urticaria
CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire
DLQI: Dermatological Life Quality Index
EAACI: European Academy of Allergology and Clinical Immunology
EDF: European Dermatology Forum
GA^{2}LEN: Global Allergy and Asthma European Network
IgE–anti-TPO: IgE antibodies against TPO
TPO: Thyroperoxidase
UAS: Urticaria activity score
UAS7: Weekly urticaria activity score
WAO: World Allergy Organization

IgG–anti-TPO levels and lymphocyte counts, as well as decreased C4 complement levels.[8]

Omalizumab is a recombinant humanized mAb that selectively binds to the C3 domain of the IgE heavy chain (ie, the site where IgE would bind to FcεRI) and thereby reduces levels of free IgE in serum.[9,10] In addition, because occupancy of FcεRI by IgE determines the levels of surface FcεRI expression, reduced binding of IgE to FcεRI leads to a downregulation of FcεRI expression on mast cells and basophils.[11-13] Thus in patients with CU with IgE antibodies against TPO, omalizumab could reduce or inhibit mast cell activation by reducing the levels of these IgE autoantibodies, decreasing IgE receptor density on cutaneous mast cells, or both. Therefore the present study was conducted to assess the efficacy of omalizumab in patients with CU who exhibit IgE antibodies against TPO. In addition, the safety and tolerability of omalizumab were also assessed.

METHODS

Study population

Male and female patients aged 18 to 70 years with a clinical diagnosis of moderate-to-severe CU (as classified by the latest consensus guidelines from the European Academy of Allergology and Clinical Immunology [EAACI], the Global Allergy and Asthma European Network [GA^{2}LEN], the European Dermatology Forum [EDF], and the World Allergy Organization [WAO][1]; ie, those with persistent symptoms for ≥6 weeks despite receiving maximal in-label antihistamine therapy) at screening, body weight between 20 and 150 kg, a total serum IgE level between 30 IU/mL or greater and 700 IU/mL or less, a specific serum IgE–anti-TPO antibody level of 5.0 IU/mL or greater within the last 3 months before randomization, and a weekly urticaria activity score (UAS) of 10 or greater at the end of screening were eligible for enrollment in the study. Serum IgE–anti-TPO levels were determined by using a site-directed human IgE capture ELISA, as previously described.[8] The UAS is a composite scoring system based on the patient's diary by using numeric severity ratings from 0 to 3 (0, none; 3, intense) for the number of wheals per 24 hours and the intensity of pruritus. The total daily score (sum of the wheal and pruritus scores) could therefore assume any value between 0 and 6.[1,14]

Patients were excluded from the study if they had acute urticaria, chronic diarrhea, severe renal dysfunction, or increased serum IgE levels for reasons other than allergy or urticaria. Patients with a history of epilepsy, allergy to antibiotics, malignancy within the past 5 years, or cerebrovascular attacks or ischemia or who had taken oral or parenteral corticosteroids, methotrexate, cyclosporine, or other immunosuppressant medications during the 4 weeks before screening were also excluded.

Study design and treatments

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 16 centers in Germany. It was approved by the ethics committee of each participating study center and was conducted in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice, the ethical principles embodied in the Declaration of Helsinki (1989), and applicable local regulations. Written informed consent was obtained from all patients before their participation in the study.

The study comprised a prescreening visit, a 3-week screening period (divided into 2 phases), and a 24-week double-blind treatment period. At the prescreening visit, informed consent was obtained, and patients were assessed for eligibility. Patients received 10 mg/d loratadine and 1 mg clemastine as rescue medication (maximum of 3 tablets per day) for 1 week during the first phase of the screening period to select for patients with CU with symptoms that cannot be controlled by maximal in-label therapy (ie, oral antihistamines). Patients demonstrating uncontrolled disease activity (UAS >0) during any of these 7 days were subsequently entered into the second phase of screening, during which they received antihistamines (10 mg of loratadine on demand and, if still symptomatic, up to 3 tablets of 1 mg/d clemastine) for 2 weeks. Those demonstrating a weekly UAS of 10 or greater at the end of the second phase of screening were subsequently entered into the randomized, double-blind treatment period.

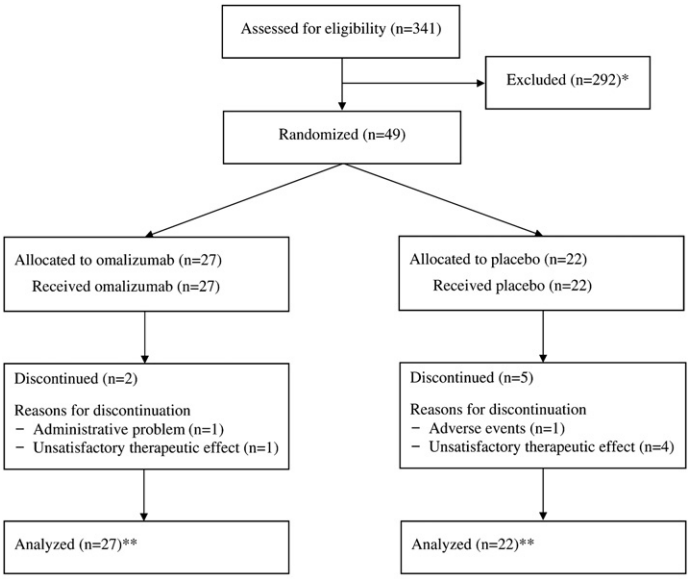
At baseline, eligible patients were randomized (1:1) to treatment with omalizumab or placebo. Randomization was performed by using a validated system that automated the random assignment of the treatments to randomization numbers in the specified ratio. Omalizumab (75-375 mg) or placebo was administered subcutaneously once every 2 or 4 weeks for 24 weeks. The doses were individualized for the patients based on their body weights and total serum IgE levels at screening and were derived from the approved asthma dosing table for omalizumab.[15] Treatment allocation was concealed from the patients, investigating staff, and clinical trial team by using study drugs that were identical in packaging, labeling, schedule of administration, and appearance.

No medications other than H_1-blocking antihistamines, such as 10 mg of loratadine on demand and 1 mg of clemastine as rescue medication, were permitted.

Assessments

During the screening and treatment periods, patients were asked to record daily scores (based on duration, size, number, and/or intensity) for wheals, pruritus, erythema, and angioedema and to report concomitant medication use (loratadine and clemastine) by using a paper diary.

Efficacy assessments included calculation of UAS from the patients' diaries. Because of frequent variations in disease intensity during the course of a day, the assessment of overall disease activity was based on a weekly aggregate UAS (ie, the sum of the daily UAS self-evaluation scores of 7 individual days, which could range between 0 and 42 per week, as described previously).[16,17] The primary efficacy end point was the change from baseline in mean weekly UAS after 24 weeks of treatment. Secondary efficacy end points included the standardized area under the curve (AUC) of UASs over 24 weeks; daily scores for wheals, pruritus, erythema, and angioedema; use of concomitant medication; and the patient's and investigator's global assessment of symptoms using a graded Likert scale (0, none; 1, mild; 2, moderate; and 3, severe). In addition, the patient's health-related quality of life was evaluated by using previously validated instruments, such as the Dermatology Life Quality Index (DLQI),[18] Skindex-29,[19] and the Chronic Urticaria Quality of Life Questionnaire (Cu-Q2oL).[20] The DLQI is a compact questionnaire consisting of 10 items under 6 headings: symptoms and feelings, daily activities, leisure, work/school, personal relationships, and treatment. Each item is scored on a 4-point scale ranging from 0 to 3. An overall DLQI score (range, 0-30) is calculated by summing the scores for each item. A higher score is considered an indicator of greater impairment in health-related quality of life.[18] Skindex-29 consists of 29 items categorized into 3 domains, including physical symptoms, social functioning, and emotional state. An overall quality-of-life index score (range, 0-100) is obtained by adding the scores from the 3 domains, with higher scores indicating poorer quality of life.[19] Although the DLQI and



* Reasons for exclusions: Patients did not meet inclusion criteria: n = 240 (IgE-anti-TPO too low: n = 160, total IgE too low: n = 51, disease activity too low: n = 19, total IgE too high: n = 5, patients did not have chronic spontaneous urticaria, but food allergies: n = 3, acute urticaria: n = 1, or exercise-induced urticaria: n = 1), recruitment was stopped before enrollment: n = 31, patients exhibited exclusion criteria: n = 11 (use of excluded medication: n = 5, withdrawal of consent: n = 2, myocardial infarction: n = 1, elevated thyroid hormones: n = 1, cancer: n = 1, dyspnoe: n = 1), lack of compliance: n = 7, and administrative reasons: n = 3.

** Both intent-to-treat and safety populations

FIG 1. Organizational flow chart.

Skindex-29 are instruments used to measure the health-related quality of life of any dermatology patient, the Cu-Q2oL has been specifically developed for use in patients with CU and encompasses the physical, emotional, social, and practical domains that characterize this condition. The German version of the Cu-Q2oL consists of 23 items categorized under the following scales: limits looks, swelling/eating, functioning, sleep, mental status, and itching/embarrassment.[20,21] Each item is scored on a 5-point Likert-type scale.

Safety assessments included the recording of adverse events (AEs) and serious AEs, along with evaluation of their severity, duration, and relationship to the study drug. In addition, urinalysis, regular monitoring of hematology and blood chemistry results, pregnancy tests, and assessment of vital signs and body weight were performed.

Statistical analyses

This trial was designed as a proof-of-concept trial with a clear focus on exploration rather than statistical testing. The sample size was chosen in a way that the test for the primary end point, the mean weekly UAS, would have 86% power by using a 2-sided 5% significance level if the treatment effect (ie, the difference between the treatment groups) was at least as large as its SD (standardized effect size, >1). This was considered a very large effect.

All efficacy analyses were performed on the intention-to-treat population, which included all randomized patients who received at least 1 dose of study drug and had postrandomization primary efficacy data. Demographic and baseline characteristics were summarized for all patients in the safety population, which consisted of all patients who received at least 1 dose of randomized study drug and had at least 1 postbaseline safety assessment. The primary end point (mean weekly UAS) was evaluated by using an analysis of covariance model with the factors of treatment and center and with the baseline score as the covariate. For the treatment contrast between omalizumab and placebo, a 95% CI and a 2-sided P value were calculated.

Similar analysis of covariance models were used to analyze the standardized UAS AUC and the daily scores for wheals, pruritus, erythema, and angioedema. The other secondary variables (the DLQI, Skindex-29, and Cu-Q2oL questionnaires; concomitant and rescue medication use; and the patient's and investigator's global symptom assessments) were summarized descriptively. AEs, laboratory data, and measurements of vital signs were summarized descriptively by treatment group. Data were analyzed with SAS version 8.2 statistical software for Windows (SAS Institute, Inc, Cary, NC).

RESULTS

Patient disposition is presented in Fig 1. Between May 2007 and May 2009, 341 patients were screened for this study; of those patients, 49 were randomized. More than 95% of the patients who were screened but not randomized were not included in the study because their total serum IgE levels were less than 30 IU/mL, their specific serum IgE–anti-TPO antibody levels were less than 5.0 IU/mL, the recruitment of patients for the study was stopped, and/or the weekly urticaria activity score (UAS7) was less than 10 (Fig 1). During the study, all patients received at least 1 dose of the assigned medication, and no patient received the study drug in error; thus the safety population was identical to the intention-to-treat population. Forty-two (85.7%) patients completed the study. Major protocol deviations were reported in 18 (36%) patients, which mainly consisted of premature discontinuations (Fig 1), lost diary data (n = 6), or deviations from the visit schedule (n = 5). Table I represents the demographics and baseline clinical characteristics of all randomized patients. The mean age of all patients was 40.5 years. All patients were white, and the majority (77.6%) of them were female. The mean IgE–anti-TPO antibody level was 6.9 ± 4.25 IU/mL.

Patients experienced a reduction in UAS7 scores from baseline to week 24 of 17.8 under omalizumab and 7.9 under placebo (least squares means); the difference of 9.9 points between treatment groups was statistically significant (95% CI, 2.7-17.1; $P = .0089$) and clinically relevant (Fig 2, *A*). The actual UAS7 values (means

TABLE I. Patients' demographics and baseline characteristics

Characteristics	Omalizumab (n = 27)	Placebo (n = 22)
Age (y), mean ± SD (range)	39.1 ± 9.0 (24-57)	42.3 ± 15.0 (20-69)
Sex, no. (%)		
Male	8 (29.6)	3 (13.6)
Female	19 (70.4)	19 (86.4)
Race, no. (%), white	27 (100.0)	22 (100.0)
Height (cm), mean ± SD (range)	171.0 ± 7.2 (160-187)	164.1 ± 6.6 (149-176)
Weight (kg), mean ± SD (range)	81.9 ± 20.2 (56-130)	71.2 ± 12.4 (51-92)
IgE–anti-TPO (IU/mL), mean ± SD	7.3 ± 4.6	6.2 ± 3.7
Total IgE (IU/mL), mean ± SD	211 ± 158	181 ± 136

± SDs) for the omalizumab group were 24.6 ± 7.4 at baseline and 6.8 ± 10.0 after treatment (placebo group: 21.3 ± 7.6 at baseline and 15.5 ± 11.0 after treatment). Fig 2, *B*, shows the mean daily UASs over the 24-week treatment period. In contrast to placebo, those receiving omalizumab experienced a marked reduction in UAS during the first week of therapy, and the mean UASs in the omalizumab group continued to decrease through week 24 (day 169). The standardized UAS AUC over 24 weeks was significantly lower for omalizumab than placebo ($P < .001$).

The number and intensity of wheals, pruritus, erythema, and angioedema were lower in those receiving omalizumab compared with those receiving placebo (see Tables E1 and E2 in this article's Online Repository at www.jacionline.org). After week 24, patients receiving omalizumab demonstrated a significant reduction in the score for wheals (least squares mean, −9.2 vs −3.3; $P = .0019$), and a complete protection from wheal development was observed in 19 (70.4%) patients in the omalizumab group compared with only 1 (4.5%) patient in the placebo group. Similarly, complete absence of pruritus, erythema, and angioedema was observed in 16 (59.3%), 18 (66.7%), and 21 (77.8%) patients, respectively, in the omalizumab group compared with only 2 (9.1%), 4 (18.2%), and 8 (36.4%) patients, respectively, in the placebo group.

Treatment with omalizumab resulted in a substantial decrease in mean concomitant medication use, from 2.9 loratadine tablets and 6 clemastine tablets taken in the 7 days before randomization to 0.3 loratadine tablets and 0.7 clemastine tablets taken during week 24 (see Fig E1 in this article's Online Repository at www.jacionline.org). The corresponding values in the placebo group for loratadine and clemastine use were 3.5 and 6.1, respectively, in the 7 days before randomization and 3.3 and 1.4, respectively, at week 24 (Fig E1).

According to patients' global assessments of symptoms, 59% of those in the omalizumab group reported being symptom free at the end of the study compared with 14% in the placebo group (Fig 3). The investigator's global assessment of the patients' symptoms corroborated the patients' own assessment of symptoms. Substantial differences were again apparent between the 2 treatment groups; 67% of patients receiving omalizumab were assessed as having achieved a complete resolution of urticaria-related symptoms after week 24 compared with 4% of placebo recipients (Fig 3).

Fig 4 and Figs E2 and E3 (available in this article's Online Repository at www.jacionline.org) show the percentage improvement in the quality of life of the study participants as measured by the DLQI, Skindex, and Cu-Q2oL questionnaires. All 3 questionnaires revealed a significantly greater improvement of quality-of-life for patients receiving omalizumab compared with placebo ($P < .01$).

The overall incidence of AEs during the treatment phase was 81.5% (22/27) with omalizumab compared with 86.4% (19/22) with placebo. The most frequent AEs (>5% of all AEs) were diarrhea (omalizumab, n = 4 [14.8%]; placebo, n = 2 [9.1%]), nasopharyngitis (omalizumab, n = 9 [33.3%]; placebo, n = 11 [50%]), and headache (omalizumab, n = 10 [37%]; placebo, n = 6 [27.3%]). The incidence of suspected drug-related AEs was similar between those receiving omalizumab and placebo (22.2% and 22.7%, respectively). One patient receiving placebo experienced SAEs (eye infection and angioedema) during the treatment phase and was withdrawn from the study. There were no deaths reported during the study. The number of patients with notable changes in laboratory values during the study was small, and there was no evidence of any clinically meaningful trends in the laboratory estimates or vital signs associated with omalizumab therapy.

DISCUSSION

An increasing number of reports demonstrating the utility of omalizumab in patients with refractory CU have appeared recently in the medical literature.[22,23] However, the majority of these are observational case reports and uncontrolled studies involving relatively few patients. We explored the clinical efficacy and safety of omalizumab in patients with CU exhibiting IgE against TPO by using a randomized, double-blind, placebo-controlled study design. The dose and dosing frequency of omalizumab were based on the total serum IgE level and body weight, which is consistent with those used for patients with allergic asthma eligible for omalizumab therapy. The results of this study showed that omalizumab significantly reduced disease activity, decreased the need for additional medication to control symptoms, and improved patients' health-related quality of life.

The significant benefit observed in IgE–anti-TPO–positive patients with CU treated with anti-IgE suggests that IgE–anti-TPO is critical for the development of urticarial symptoms in these patients and that anti-IgE protects from urticarial symptoms by reducing IgE–anti-TPO autoantibodies. Further studies, such as skin testing or mast cell activation studies, are needed to confirm and prove that IgE–anti-TPO does induce mast cell degranulation and urticarial symptoms. Further studies are also needed to test IgE–anti-TPO–negative patients with urticaria for their response to anti-IgE treatment and to explain the mechanisms and speed of action of anti-IgE in IgE–anti-TPO–positive patients with CU. The current EAACI/GA^{2}LEN/EDF/WAO guidelines[1] recommend assessing disease activity in patients with CU by using 24-hour self-evaluation scores based on the UAS system. In this study we used weekly UASs to evaluate overall disease activity. The decrease in mean weekly UASs with omalizumab in this study was 3 times that of placebo. A decrease in UASs was observed during the first week of therapy and continued until the end of the study. This rapid improvement in disease activity was observed in previous studies as well. Significant clearing of urticaria within 1 week of starting omalizumab therapy was reported by Spector and Tan[24] in patients with refractory CU who had earlier received different combinations of antihistamines, antileukotrienes, H_2-blockers, and lipoxygenase inhibitors with little or no success. In this case series, however, omalizumab

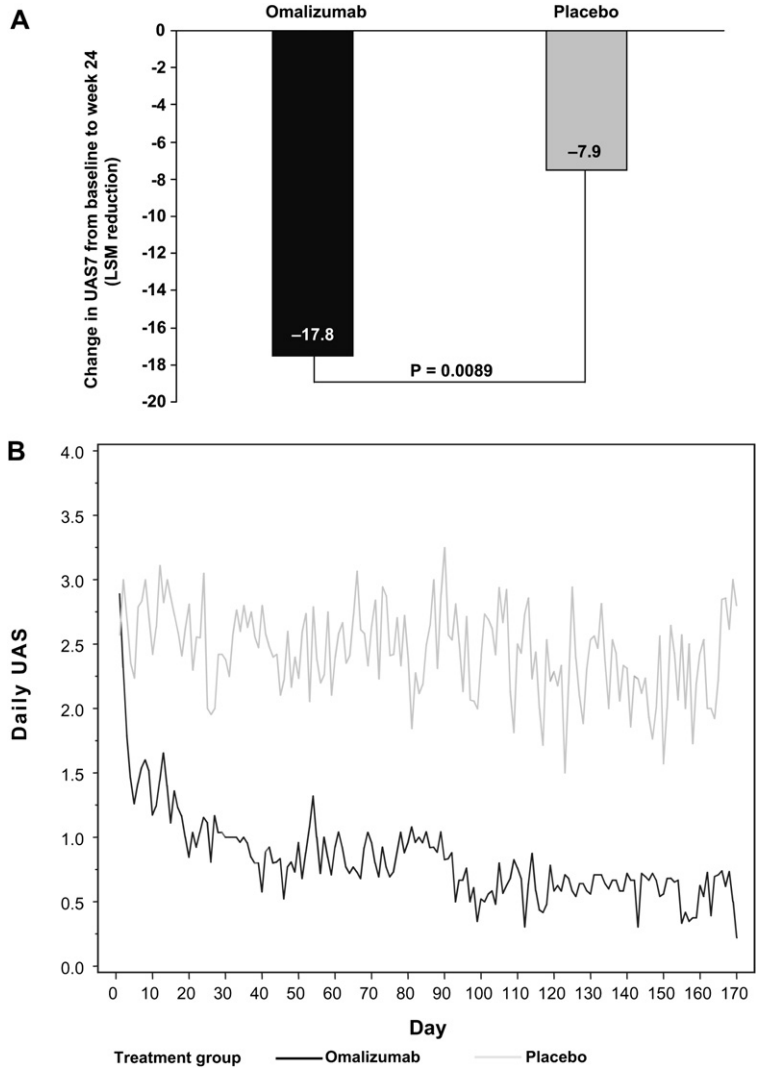


FIG 2. **A**, Change in UASs after 24 weeks of treatment. Difference between omalizumab and placebo = −9.9 (95% CI, 2.7-17.1). Population for analysis: intention-to-treat population. Analysis of covariance model: variables = baseline, center, and treatment. Least squares mean after adjusting the covariates, such as center, baseline value, and treatment group. **B**, Mean daily UAS. The standardized UAS over 24 weeks was significantly lower for omalizumab than placebo (P = .0002). Population for analysis: intention-to-treat population.

was used at higher doses than recommended in patients with allergic asthma.

In this study, in addition to significant reductions in weekly UASs, omalizumab resulted in complete protection against the appearance of wheals in 70% of the treated patients based on data from the patients' diaries. Similar observations were made with regard to the complete resolution of pruritus, erythema, and angioedema. In addition, according to the patients' global assessment of symptoms, more than half of those in the omalizumab group were symptom free at the end of the study compared with approximately one tenth of those in the placebo group. These observations were paralleled by the investigator's global assessment of symptoms. Kaplan et al[25] studied the effects of omalizumab in 12 patients with chronic autoimmune urticaria refractory to antihistamine therapy. Approximately 60% of these patients achieved complete remission by the end of the 16-week treatment period. Furthermore, in a case report of a patient with severe CU for about 10 years,[26] the first injection of omalizumab yielded 90% control of symptoms, and after the second injection, which was administered 4 weeks after the first, the patient was totally symptom free.

The frequency of use of rescue medication for symptomatic relief provides an indication of the degree of clinical impairment. Kaplan et al[25] reported a significant decrease in rescue medication use from baseline to the conclusion of their study in patients receiving omalizumab ($P = .004$). In our study treatment with omalizumab markedly reduced the burden of repeated rescue medication use. The use of omalizumab was associated with an overall reduction in the use of loratadine and clemastine from 3 and 6 times, respectively, per week at the beginning of the study to less than once a week at the end of the treatment period.

Available data suggest that CU has a detrimental effect on both objective functioning and subjective well-being.[2] Furthermore, both health status and subjective satisfaction are lower in patients with CU than in healthy subjects and patients with respiratory

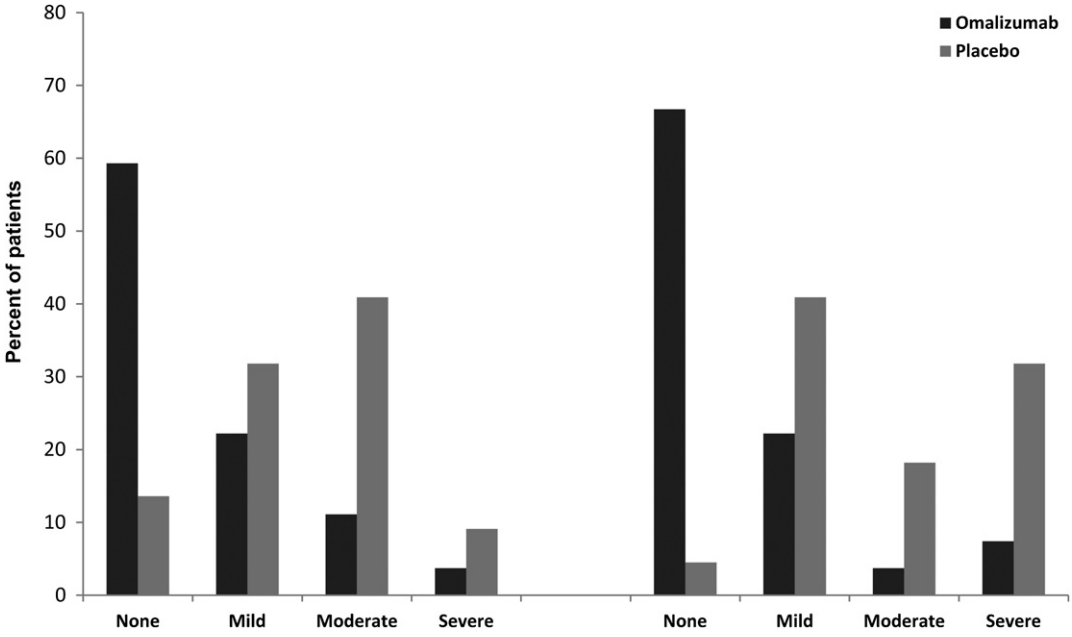


FIG 3. Patients' and investigator's global assessment of symptoms at study's end. Population for analysis: intention-to-treat population.

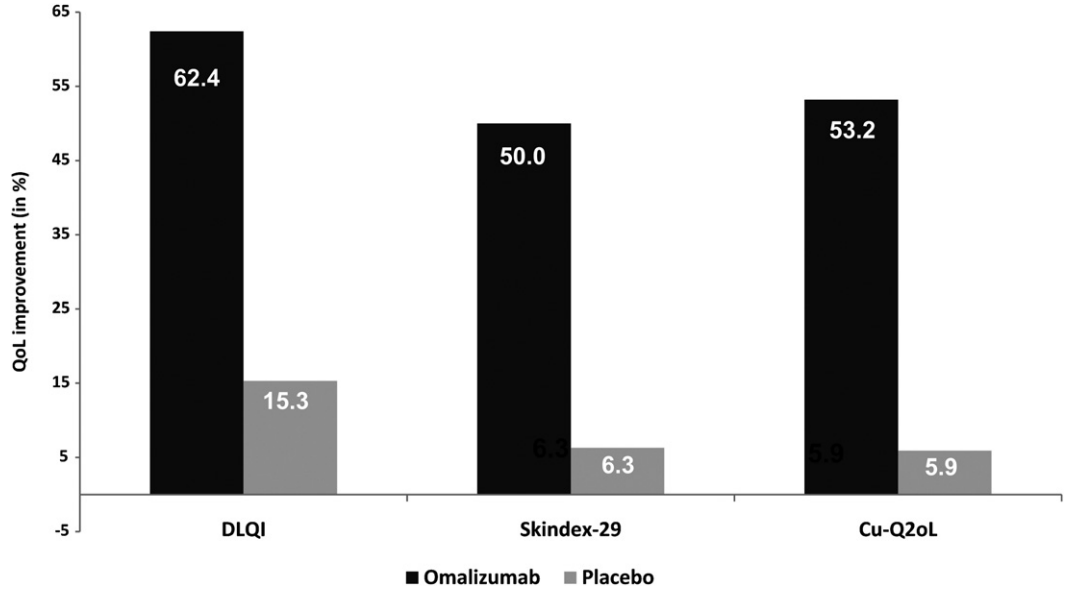


FIG 4. Percentage improvement in quality of life *(QoL)*. Population for analysis: intention-to-treat population.

allergies.[27] By providing rapid control of symptoms and decreasing the burden of additional medications, omalizumab can provide benefits that are relevant to patients, offering them the prospect of significant amelioration of their disease experience. Indeed, assessment of health-related quality of life by using evaluative instruments specifically designed for skin diseases, such as the DLQI and Skindex-29, suggested that the observed clinical benefits with omalizumab might translate into improvements in the patients' quality of life. In particular, the DLQI and Skindex assessments revealed a significantly greater improvement of 45% to 50% in the quality of life of patients receiving omalizumab compared with 6% to 11% in those receiving placebo. Similar improvements in the functional capacity and well-being of patients with CU have been demonstrated previously by using the DLQI[25] and Skindex-29[28] questionnaires.

A banding system has been suggested to assist the clinical interpretation of DLQI scores.[29] Based on this system, in the current study omalizumab decreased the influence of CU on the patients' lives from a very large effect to a small one. On the contrary, there was no such change in patients receiving placebo. Moreover, in patients with CU, a difference in overall DLQI scores in the range of 2.24 to 3.10 has been proposed as a minimal

clinically important difference.[30] In this study the mean change in DLQI scores between omalizumab and placebo after week 24 was 4.8, which exceeded the minimum clinically important difference. In addition, assessment of the effect of treatment on the individual Skindex-29 domains also demonstrated that all scores were significantly improved after 24 weeks of treatment with omalizumab in contrast to placebo, with the degree of improvement of functional impairment being similar to the improvement in the burden on symptoms and emotions.

In addition to the DLQI and Skindex questionnaires, a disease-specific questionnaire, namely CU-Q2oL, was used in this study. The results observed with the CU-Q2oL questionnaire (55% improvement with omalizumab vs 6% with placebo) were similar to those seen with the DLQI and Skindex questionnaires, indicating a significant enhancement in the overall quality of life of patients with CU receiving omalizumab but no meaningful improvement in those treated with placebo. Interestingly, the distribution of the different CU-Q2oL domain scores indicated that the extent of improvement with omalizumab was of a higher magnitude on the functioning and itching/embarrassment item bundles than on the other scales. Each of the CU-Q2oL scales discriminated clearly between omalizumab and placebo, with the effect sizes for omalizumab being markedly superior to those for placebo.

In terms of overall safety, all treatments in this study were safe and well tolerated. The overall rate of AEs was comparable between omalizumab and placebo. The most frequent AEs were nasopharyngitis, diarrhea, and headache. In patients with allergic airway disease, local injection-site symptoms, most commonly bruising and itching, and anaphylaxis, presenting as bronchospasm, hypotension, or syncope, have been reported to occur after subcutaneous administration of omalizumab[31,32]; the incidence of such AEs in this study was very low or nil. In addition, there were no safety concerns with regard to any of the laboratory parameters or any clinically relevant differences in vital signs between the treatment groups.

Taken together, the results of our study indicate a consistency in the effect of omalizumab across all defined outcome measures, which underlines the internal validity of the study and suggests that omalizumab might be a useful therapeutic option in patients with CU with high levels of IgE–anti-TPO autoantibodies. Other related clinical scenarios in which omalizumab has shown promise include cold urticaria,[33] cholinergic urticaria,[34] solar urticaria,[35,36] heat urticaria,[37,38] and symptomatic dermographisms.[39] However, it should be emphasized that omalizumab is currently not an approved treatment modality for these conditions, and the potential side effects of this medication, including the risk for anaphylaxis, should be evaluated thoroughly.[22]

In conclusion, the results of this study demonstrate that omalizumab is an effective treatment option for patients with CU. In addition, omalizumab had a good overall safety and tolerability profile in these patients. The results of this study support the recommendation of the latest EAACI/GA^{2}LEN/WAO/EDF guidelines[2] to use omalizumab in the treatment of patients with CU who do not sufficiently respond to standard therapy.

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Clinical implications: Omalizumab shows strong efficacy and a very good safety profile in the treatment of patients with CU with IgE autoantibodies against TPO.

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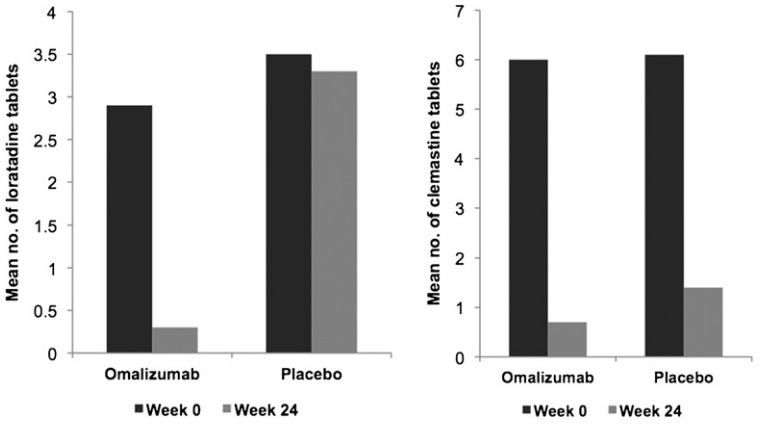

FIG E1. Reduction in concomitant and rescue medication use from baseline to week 24. Population for analysis: intention-to-treat population.

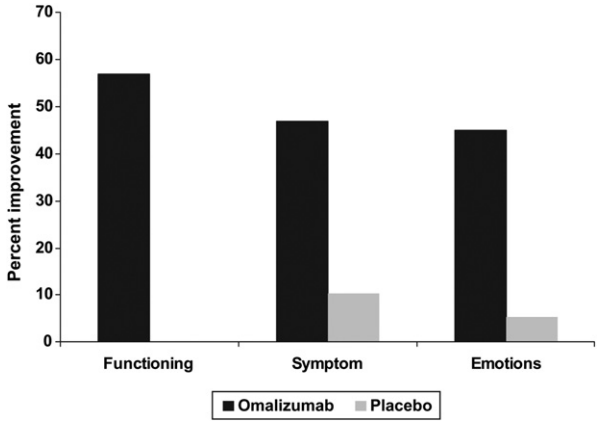

FIG E2. Percentage improvement in the quality-of-life subdomains of the Skindex questionnaire. Population for analysis: intention-to-treat population.

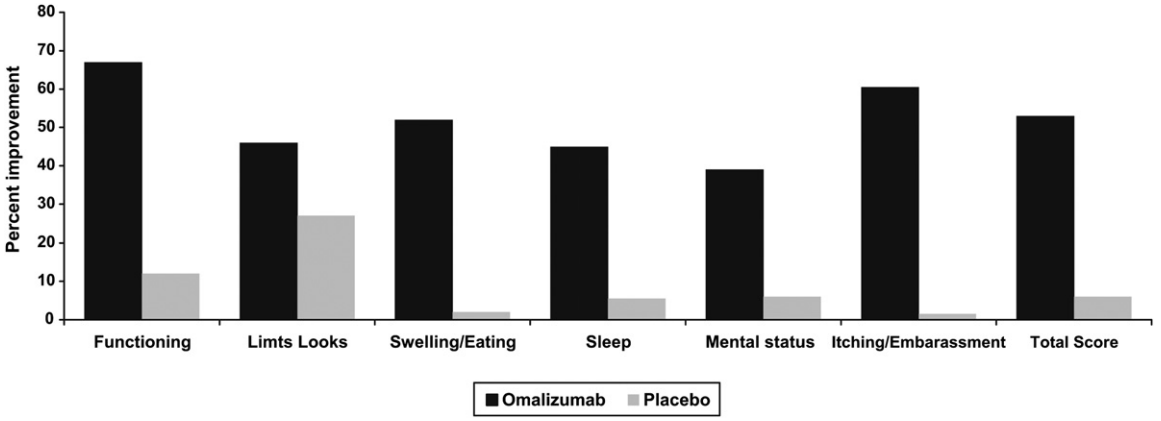

FIG E3. Percentage improvement in the subdomains of the Cu-Q2oL. Population for analysis: intention-to-treat population.

TABLE E1. Number of wheals and episodes of erythema during week 24 of treatment

	Wheals		Erythema	
	Omalizumab, no. (%)	Placebo, no. (%)	Omalizumab, no. (%)	Placebo, no. (%)
None	19 (70.4)	1 (4.5)	18 (66.7)	4 (18.2)
<10	3 (11.1)	11 (50.0)	4 (14.8)	7 (31.8)
10-50	1 (3.7)	3 (13.6)	1 (3.7)	4 (18.2)
>50	1 (3.7)	1 (4.5)	1 (3.7)	1 (4.5)

Population for analysis: intention-to-treat population; missing assessments not included.

TABLE E2. Intensity of pruritus and angioedema during week 24 of treatment

	Pruritus		Angioedema	
	Omalizumab, no. (%)	Placebo, no. (%)	Omalizumab, no. (%)	Placebo, no. (%)
None	16 (59.3)	2 (9.1)	21 (77.8)	8 (36.4)
Mild	4 (14.8)	8 (36.4)	1 (3.7)	6 (27.3)
Moderate	3 (11.1)	3 (13.6)	0 (0.0)	1 (4.5)
Severe	1 (3.7)	3 (13.6)	2 (7.4)	1 (4.5)

Population for analysis: intention-to-treat population; missing assessments not included.